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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/442,277	05/16/95	BUYSE E	6287-026

18N2/0122

PENNIE & EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2711

EXAMINER	
STANTON, B	
ART UNIT	**PAPER NUMBER**
1819	

DATE MAILED: 01/22/97

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary

Application No.	Applicant(s)
08/442,277	Boyse et al.
Examiner	**Group Art Unit**
Brian R. Stanton	1819

☒ Responsive to communication(s) filed on *10/30/96 and 11/18/96*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *Three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *60-62, 67-102, and 104-111* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *60-62, 67-102, and 104-111* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1819.

The instant application is a continuation of Application Serial No. 07/950,356, filed 9/24/92, now abandoned, which is a continuation of Application Serial No. 07/269,926, filed 11/10/88, now U.S. Patent No. 5,192,553, which is a continuation-in-part of Application Serial No. 07/119,746, filed 11/12/87, now U.S. Patent No. 5,004,681.

The responsive amendment filed 10/30/96 (Paper No. 8) with its attached exhibits have been entered. Claims 10, 60-62, 67-102 and 104-111 remain pending in the instant Application.

The terminal disclaimer over U.S. Patent Serial No. 5,192,553, filed 11/18/96 has been entered and is proper.

The following is a new grounds of rejection.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 60 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 60 of copending application Serial No. 08/443,221. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

Claims 105-109 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new grounds of rejection.

Claims 105-109 are vague and indefinite because claim 105 depends from itself and claims 106, 107, and 109 depend from claim 105. Similarly, claim 108 depends from itself. In the interests of compact prosecution and based upon the context of the pending claims, claim 105-109 have been treated as if they depended from claim 104.

Claims 60-62, 67-102 and 104-111 stand rejected under 35 U.S.C. § 103 as being unpatentable over Nakahata et al., 1982 (DX), Saunders, 1965 (AN) and either of Ende, 1966 (BV) or Ende et al., 1972 (BU), the preceding combination in view of Applicant's admissions on pages 10, 11, 27 and 28, Herzig et al., 1983 (CQ), McGlave et al., 1985 (DT) and Fabian et al., 1982 (BW) for reasons of record advanced in the preceding Office Action mailed 4/30/96 (Paper No. 6). Applicant's arguments filed 10/30/96 and 11/18/96 have been fully considered but they are not persuasive.

Applicant reminds the examiner of the legal standard of obviousness in Paper No. 8 at pages 8 and 9. In response, it is noted that it is these standards that have been applied in the instant finding of obviousness.

Applicant asserts that the examiner must have employed hindsight reasoning in the finding of obviousness. However, the instant invention is drawn to the use of a product which was known in the art to have been useful for the claimed purpose and therefore the rationale supporting the instant grounds of obviousness was found in the prior art of record and is therefore not a result of hindsight reasoning.

Applicant summarizes that the claimed invention is drawn to hematopoietic reconstitution which requires long-term, complete reconstitution of the immune system *in vivo*. However, the pending claims are only drawn to methods of treatment rather than any long term reconstitution and the prior art of record as exemplified by Nakahata et al. indicates that fetal cord blood would have been expected to have

comprised hematopoietic stem and progenitor cells similar to adult bone marrow. Since adult bone marrow was known to have been useful in the reconstitution of lethally irradiated subjects, the artisan, based upon the similarity between adult bone marrow and fetal cord blood, would have expected that fetal cord blood would have been useful in hematopoietic reconstitution as defined by applicant.

Applicant argues that none of the cited prior art indicates that one would have been motivated to have used cryopreserved blood in treatments of hematopoietic insufficiencies. However, no indication has been made that supports that cryopreserved blood is any different from any other type of blood.

Applicant argues that since fetal cord blood was often discarded that the artisan did not recognize its usefulness. However, Nakahata et al. indicates that the artisan was interested in fetal cord blood and recognized its properties.

Applicant argues that the teachings of the instant specification are required to have imputed a reasonable expectation of success in using human neonatal cord or fetal blood in treatments. However, the pending claims only require the use of such blood in a treatment and since such blood would, at a minimum, have been expected to have been useful as a blood replacement in, for example, infants, one would have reasonably expected it to have been useful in treatments. Further, Nakahata indicates that its composition would have included cells that would have made it more useful that circulating adult blood.

Applicant presents a number of arguments relating to the composition of fetal blood that one would not have recognized. In response, it is first noted that such properties would have been expected and secondly, even if such were not recognized, one would still have expected that blood, regardless of its source, would have been useful as part of a blood placement treatment regimen.

Applicant reviews the teachings of the prior art applied in the instant grounds of rejection and returns to the argument that one would not have reasonably expected hematopoietic reconstitution. However, it is reiterated that as pending the claims only require a treatment method rather than hematopoietic reconstitution. Further, while applicant characterizes the teaching of Nakahata as failing to disclose that stem cells are present in fetal cord blood, such is not a requirement for the artisan to have

expected that a variety of hematopoietic lineages would have been reconstitutable using fetal cord blood as donor tissue. While neither the prior art nor applicant has demonstrated complete hematopoietic reconstitution of lethally irradiated hosts, such a demonstration is not necessary to support the instant ground of rejection. First, one would have been motivated to have used any blood composition that contained greater proportions of hematopoietic progenitor cells and second it is impossible to prove "complete" hematopoietic reconstitution because the "complete" repertoire of the blood is undefined.

Applicant argues that the use of non-cryopreserved blood would not have motivated one to have used cryopreserved blood. However, cryopreservation was a known means of keeping cells viable for an extended period of time and therefore would have been expected to have been equivalent to non-cryopreserved blood. In the absence of any indication of any material difference between cryopreserved and non-cryopreserved blood there is simply no way to distinguish the two compositions.

Applicant refers to a letter to the editor by Drs. Ends and Ends (see Paper No. 8, at pages 14 and 15) wherein it was indicated that umbilical cord blood had been used as early as 1972. However, such reference indicates that the potentiality of the use of cord blood was recognized. Applicant continues in the paragraph bridging pages 15 and 16, that in response to this letter to the editor, the editor, Dr. Gale, indicates a lack of expectation of success in using cord blood. However, in reviewing the entirety of the quotation in the latter paragraph of Paper No. 8, it is noted that Dr. Gale was referring to the use of non H.A. typed blood in combination with mild chemotherapy. After stating the conditions, only then does Dr. Gale state "I would not expect engraftation to occur **under these conditions**...". Clearly, the conditions were critical to Dr. Gale's assessment of the transplantation using cord blood.

Applicant continues on page 16, first full paragraph of Paper No. 8, to indicate that disinterested third parties would only believe that cord blood would have been useful for temporary transfusion. However, even a temporary transfusion would be considered a treatment as required by the pending claims.

Applicant continues in the characterization of the teachings of the prior art on pages 16 and 17 by again indicating a failure of the prior art to indicate unequivocal complete hematopoietic reconstitution. However, such is not required for the claimed invention and has not been demonstrated in the instant application.

Applicant refers to the second Bernstein declaration which has been submitted as an unexecuted exhibit on 10/30/96 (Paper No. 9). In the reference and discussion of this declaration applicant points to the discussion in Paragraph 30 which relates to the expectation of the ability of fetal blood as an agent of long term hematopoietic reconstitution. In this discussion, a lack of relationship between adult bone marrow and fetal blood is advanced as is Bernstein's personal lack of expectation of the use of fetal blood as a long term reconstituting agent. However, no requirement for such reconstitution is required by the claimed invention.

Applicant argues that numerous sources evidence that different sources of stem cells were not considered equivalent or interchangeable. However, while the teachings presented by Applicant in Paper No. 8 at pages 20 and 21 support that all stem cell sources were not identical, such teachings do not indicate that they are not all useful in various treatment regiments. While one source may be better than another, such differences were recognized in the art (as supported by applicant's arguments) and support a finding that the artisan would have used any of a variety of hematopoietic cells in a variety of treatment regimens and would have been able to have determined which sources of hematopoietic stem/progenitor cells were appropriate for which treatment regimen.

Applicant refers to a reference by Thompson, 1995, entitled "Umbilical Cords: Turning Garbage Into Clinical Gold" and uses this reference to support the contention that one viewed umbilical cord blood as waste rather than a clinically useful treatment agent. However, reference to the cited article (reference IB) at the first and second paragraphs, deals predominantly with the recognition of the high number of CD34 positive cells representing early hematopoietic cells. While such advantages may have been recognized after the filing of the instant application, the artisan would have been motivated, at a minimum,

to have used cord blood for other reasons and in other treatment modalities and therefore would have practiced what is claimed.

On pages 23 and 24 of Paper No. 8, applicant cites a number of references that indicate that one did not have appropriate assays to determine numbers of hematopoietic repopulating cells and that therefore one would not have had a reasonable expectation that one could have performed hematopoietic reconstitution. These arguments have been amply addressed above and it is reiterated that the invention as instantly claimed is not concordant with applicant's apparent (although unsupported) assertion of unexpected results.

Applicant returns to the issue of the use of cryopreserved cells in the paragraph bridging pages 24 and 25 of Paper No. 8 and asserts that the teachings of the prior art disclosures used in the basis of the instant grounds are limited to the use of cryopreserved bone marrow cells and would not have been extendable to the use of cryopreserved fetal hematopoietic cells. Applicant further asserts that cells from different sources have different sensitivities to cryopreservation. In support of the latter assertion, applicant refers to articles relating to cryopreservation of liver cells (see Paper No. 8 at page 15). However, while it is granted that different cells have different sensitivities to freezing, the issue at hand is whether the **same** cells from a different source would have had a different sensitivity to freezing such that the artisan would not have expected them to have been useful once frozen. In this regard, applicant has not shown any material difference in the cells themselves that would have led the artisan to have had a less than reasonable expectation of success in using said cells once frozen.

Applicant continues beginning on page 25 of Paper No. 8 to address secondary considerations relating to a finding of obviousness. The first such consideration addressed relates to long felt need. In this regard, applicant indicates that a source of stem cells having properties associated with fetal tissue has long been sought. However, such a need was had been addressed by various means such as autologous transplantation, use of identical twin donors, and the like. Since fetal tissue would have been expected to

have been similar in many regards to the use of adult bone marrow, the "need" addressed by the use of fetal tissue had been addressed in the prior art.

Applicant continues by reference to the second Bernstein declaration (Paper No. 9, attachment), which indicates that no wholly satisfactory alternative to the use of bone marrow had been found until the time of the instant application. However, no demonstration is of record that shows that the use of fetal blood was "wholly" satisfactory, thereby providing a solution as an ultimate blood donor tissue. While applicant continues on pages 29-33 by discussing the various disadvantages of the use of donor bone marrow, such advantages and disadvantages were recognized by the artisan, and no evidence or showing suggests that the use of fetal tissue "solves" all of these issues. Rather, the advantages detailed in the second Bernstein declaration as quoted in Paper No. 8 at page 33 and discussed on pages 34 and 35 are advantages that would have been recognized by the artisan since they are based upon the known properties of fetal tissue.

Beginning on page 36 of Paper No. 8, applicant characterizes the "Skepticism and Disbelief in the Art" as related to the use of fetal tissue. In this discussion which ensues on pages 38 through the top of page 48, details the teachings of a variety of pre- and post-filing references that relate to the advantages that are incumbent upon the use of fetal tissue and the concordant use of such tissue in a variety of hematopoietic reconstitution protocols. These teachings are not disputed. However, such "unexpected" results that would constitute evidence of non-obviousness need to be related to the invention as claimed. In the instant case, the claimed invention is drawn to a method of treatment. Applicant's evidence suggests that the artisan was motivated to have used fetal blood in treatment modalities. The results and advantages as evidenced by applicant are, as a whole, drawn to hematopoietic reconstitution, which is not what is claimed. The artisan clearly expected to have been able to have "treated" patients with fetal tissue whether or not they would have expected that they would have been able to have performed hematopoietic reconstitution.

Beginning on page 49 and extending through page 54 of Paper No. 8, applicant refers to an unexpected result relating to graft versus host disease. However, again, while such results may have been a result of an otherwise apparent and obviousness treatment, the claimed invention is not limited to such a result. The references to the expectation of success and the unexpected results only address a species of the broader genus currently claimed and without language limiting the claimed invention to such species of the claimed invention as argued as nonobvious by applicant, the invention as pending is maintained as being *prima facie* obvious due to its broad scope relating only to a general requirement as a treatment.

Applicant argues an improper use of hindsight reasoning because there was no reasonable expectation of success in performing hematopoietic reconstitution. However, again, the claims are not limited to such an invention.

For the foregoing reasons and based upon the scope of the pending claimed invention, it is therefore maintained that the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

No claims are currently allowable.

Papers related this application may be submitted to the Group 1800 by facsimile transmission. Papers should be Faxed to the Group 1800 via the PTO FAX center located in Crystal Mall I. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (30 November 1989). The CM1 Fax Center Number is (703) 308-0294.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian R. Stanton whose telephone number is (703) 308-2801. The examiner can normally be reached on Monday through Thursday from 6:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers can be reached on (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1096.

Brian R. Stanton, Ph.D.
January 21, 1997

BRIAN R. STANTON
PRIMARY EXAMINER
GROUP 1800